CEFTIN® Tablets

(cefuroxime axetil tablets)

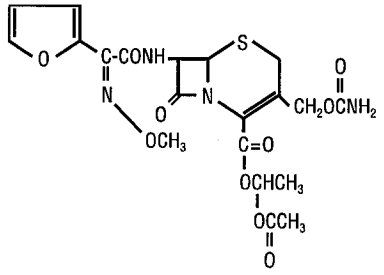
CEFTIN® for Oral Suspension

(cefuroxime axetil powder for oral suspension)

DESCRIPTION: CEFTIN Tablets and CEFTIN for Oral Suspension contain cefuroxime as cefuroxime axetil. CEFTIN is a semisynthetic, broad-spectrum cephalosporin antibiotic for oral administration.

Chemically, cefuroxime axetil, the 1-(acetyloxy) ethyl ester of cefuroxime, is (*RS*)-1-hydroxyethyl (6*R*,7*R*)-7-[2-(2-furyl)glyoxylamido]-3-(hydroxymethyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate, 7[2]-(*Z*)-(*O*-methyl-oxime), 1-acetate 3-carbamate. Its molecular formula is $C_{20}H_{22}N_4O_{10}S$, and it has a molecular weight of 510.48.

Cefuroxime axetil is in the amorphous form and has the following structural formula:



CEFTIN Tablets are film-coated and contain the equivalent of 125, 250, or 500 mg of cefuroxime as cefuroxime axetil. CEFTIN Tablets contain the inactive ingredients colloidal silicon dioxide, croscarmellose sodium, FD&C Blue No. 1 (250- and 500-mg tablets only), hydrogenated vegetable oil, hydroxypropyl methylcellulose, methylparaben, microcrystalline cellulose, propylene glycol, propylparaben, sodium benzoate (125-mg tablets only), sodium lauryl sulfate, and titanium dioxide.

CEFTIN for Oral Suspension, when reconstituted with water, provides the equivalent of 125 mg or 250 mg of cefuroxime (as cefuroxime axetil) per 5 mL of suspension. CEFTIN for Oral Suspension contains the inactive ingredients povidone K30, stearic acid, sucrose, and tutti-frutti flavoring.

CLINICAL PHARMACOLOGY:

Absorption and Metabolism: After oral administration, cefuroxime axetil is absorbed from the gastrointestinal tract and rapidly hydrolyzed by nonspecific esterases in the intestinal mucosa and blood to

cefuroxime. Cefuroxime is subsequently distributed throughout the extracellular fluids. The axetil moiety is metabolized to acetaldehyde and acetic acid.

Pharmacokinetics: Approximately 50% of serum cefuroxime is bound to protein. Serum pharmacokinetic parameters for CEFTIN Tablets and CEFTIN for Oral Suspension are shown in Tables 1 and 2.

Table 1: Postprandial Pharmacokinetics of Cefuroxime Administered as CEFTIN Tablets to Adults*

Dose† (Cefuroxime Equivalent)	Peak Plasma Concentration (mcg/mL)	Time of Peak Plasma Concentration (h)	Mean Elimination Half-Life (h)	AUC (mcg-h mL)
125 mg	2.1	2.2	1.2	6.7
250 mg	4.1	2.5	1.2	12.9
500 mg	7.0	3.0	1.2	27.4
1000 mg	13.6	2.5	1.3	50.0

* Mean values of 12 healthy adult volunteers.

† Drug administered immediately after a meal.

Table 2: Postprandial Pharmacokinetics of Cefuroxime Administered as CEFTIN for Oral Suspension to Pediatric Patients*

Dose† (Cefuroxime Equivalent)	n	Peak Plasma Concentration (mcg/mL)	Time of Peak Plasma Concentration (h)	Mean Elimination Half-Life (h)	AUC (mcg-h mL)
10 mg/kg	8	3.3	3.6	1.4	12.4
15 mg/kg	12	5.1	2.7	1.9	22.5
20 mg/kg	8	7.0	3.1	1.9	32.8

* Mean age = 23 months.

† Drug administered with milk or milk products.

Comparative Pharmacokinetic Properties: A ~~250-mg/5-mL dose~~ 250-mg/5-mL dose of CEFTIN Suspension is bioequivalent to ~~two~~ 2 times ~~125-mg/5-mL dose~~ 125-mg/5-mL dose of CEFTIN Suspension when administered with food (see Table 3). **CEFTIN for Oral Suspension was not bioequivalent to CEFTIN Tablets when tested in healthy adults. The tablet and powder for oral suspension formulations are NOT substitutable on a mg/mg basis.** The area under the curve for the suspension averaged 91% of that for the tablet, and the peak plasma concentration for the suspension averaged 71% of

the peak plasma concentration of the tablets. Therefore, the safety and effectiveness of both the tablet and oral suspension formulations had to be established in separate clinical trials.

Table 3: Pharmacokinetics of Cefuroxime Administered as 250 mg/5 mL or 2 x 125 mg/5 mL CEFTIN for Oral Suspension to Adults* With Food

Dose (Cefuroxime Equivalent)	Peak Plasma Concentration (mcg/mL)	Time of Peak Plasma Concentration (h)	Mean Elimination Half-Life (h)	AUC (mcg-h mL)
250 mg/5 mL	2.23	3	1.40	8.92
2 x 125 mg/5 mL	2.37	3	1.44	9.75

*Mean values of 18 healthy adult volunteers.

Food Effect on Pharmacokinetics: Absorption of the tablet is greater when taken after food (absolute bioavailability of CEFTIN Tablets increases from 37% to 52%). Despite this difference in absorption, the clinical and bacteriologic responses of patients were independent of food intake at the time of tablet administration in ~~two~~ 2 studies where this was assessed.

All pharmacokinetic and clinical effectiveness and safety studies in pediatric patients using the suspension formulation were conducted in the fed state. No data are available on the absorption kinetics of the suspension formulation when administered to fasted pediatric patients.

Renal Excretion: Cefuroxime is excreted unchanged in the urine; in adults, approximately 50% of the administered dose is recovered in the urine within 12 hours. The pharmacokinetics of cefuroxime in the urine of pediatric patients have not been studied at this time. Until further data are available, the renal pharmacokinetic properties of cefuroxime axetil established in adults should not be extrapolated to pediatric patients.

Because cefuroxime is renally excreted, the serum half-life is prolonged in patients with reduced renal function. In a study of 20 elderly patients (mean age = 83.9 years) having a mean creatinine clearance of 34.9 mL/min, the mean serum elimination half-life was 3.5 hours. Despite the lower elimination of cefuroxime in geriatric patients, dosage adjustment based on age is not necessary (see PRECAUTIONS: Geriatric Use).

Microbiology: The *in vivo* bactericidal activity of cefuroxime axetil is due to cefuroxime's binding to essential target proteins and the resultant inhibition of cell-wall synthesis.

Cefuroxime has bactericidal activity against a wide range of common pathogens, including many beta-lactamase–producing strains. Cefuroxime is stable to many bacterial beta-lactamases, especially plasmid-mediated enzymes that are commonly found in enterobacteriaceae.

Cefuroxime has been demonstrated to be active against most strains of the following microorganisms both *in vitro* and in clinical infections as described in the INDICATIONS AND USAGE section (see INDICATIONS AND USAGE section).

Aerobic Gram-positive Microorganisms:

Staphylococcus aureus (including beta-lactamase–producing strains)
Streptococcus pneumoniae
Streptococcus pyogenes

Aerobic Gram-negative Microorganisms:

Escherichia coli
Haemophilus influenzae (including beta-lactamase–producing strains)
Haemophilus parainfluenzae
Klebsiella pneumoniae
Moraxella catarrhalis (including beta-lactamase–producing strains)
Neisseria gonorrhoeae (including beta-lactamase-producing strains)

Spirochetes:

Borrelia burgdorferi.

Cefuroxime has been shown to be active *in vitro* against most strains of the following microorganisms; however, the clinical significance of these findings is unknown.

Cefuroxime exhibits *in vitro* minimum inhibitory concentrations (MICs) of 4.0 mcg/mL or less (systemic susceptible breakpoint) against most (≥90%) strains of the following microorganisms; however, the safety and effectiveness of cefuroxime in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled trials.

Aerobic Gram-positive Microorganisms:

Staphylococcus epidermidis
Staphylococcus saprophyticus
Streptococcus agalactiae

NOTE: Certain strains of enterococci, e.g., *Enterococcus faecalis* (formerly *Streptococcus faecalis*), are resistant to cefuroxime. Methicillin-resistant staphylococci are resistant to cefuroxime.

Aerobic Gram-negative Microorganisms:

Morganella morganii
Proteus inconstans
Proteus mirabilis
Providencia rettgeri

NOTE: *Pseudomonas* spp., *Campylobacter* spp., *Acinetobacter calcoaceticus*, and most strains of *Serratia* spp. and *Proteus vulgaris* are resistant to most first- and second-generation cephalosporins. Some strains of

Morganella morganii, *Enterobacter cloacae*, and *Citrobacter* spp. have been shown by *in vitro* tests to be resistant to cefuroxime and other cephalosporins.

Anaerobic Microorganisms:

Peptococcus niger

NOTE: Most strains of *Clostridium difficile* and *Bacteroides fragilis* are resistant to cefuroxime.

Susceptibility Tests: ***Dilution Techniques:*** Quantitative methods that are used to determine MICs provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure uses a standardized dilution method[1] (broth, agar, or microdilution) or equivalent with cefuroxime powder. The MIC values obtained should be interpreted according to the following criteria:

MIC (mcg/mL)	Interpretation
≤4	(S) Susceptible
8-16	(I) Intermediate
≥32	(R) Resistant

A report of "Susceptible" indicates that the pathogen, if in the blood, is likely to be inhibited by usually achievable concentrations of the antimicrobial compound in blood. A report of "Intermediate" indicates that inhibitory concentrations of the antibiotic may be achieved if high dosage is used or if the infection is confined to tissues or fluids in which high antibiotic concentrations are attained. This category also provides a buffer zone that prevents small, uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that usually achievable concentrations of the antimicrobial compound in the blood are unlikely to be inhibitory and that other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control microorganisms. Standard cefuroxime powder should give the following MIC values:

Microorganism	MIC (mcg/mL)
Escherichia coli ATCC 25922	2-8
Staphylococcus aureus ATCC 29213	0.5-2

Diffusion Techniques: Quantitative methods that require measurement of zone diameters provide estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2] that has been recommended (for use with disks) to test the susceptibility of microorganisms to cefuroxime uses the 30-mcg cefuroxime disk. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for cefuroxime.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 30-mcg cefuroxime disk should be interpreted according to the following criteria:

Zone Diameter (mm)	Interpretation
≥23	(S) Susceptible
15-22	(I) Intermediate
≤14	(R) Resistant

Interpretation should be as stated above for results using dilution techniques.

As with standard dilution techniques, diffusion methods require the use of laboratory control microorganisms. The 30-mcg cefuroxime disk provides the following zone diameters in these laboratory test quality control strains:

Microorganism	Zone Diameter (mm)
Escherichia coli ATCC 25922	20-26
Staphylococcus aureus ATCC 25923	27-35

INDICATIONS AND USAGE:

NOTE: CEFTIN TABLETS AND CEFTIN FOR ORAL SUSPENSION ARE NOT BIOEQUIVALENT AND ARE NOT SUBSTITUTABLE ON A MG/MG BASIS (SEE CLINICAL PHARMACOLOGY).

CEFTIN Tablets: CEFTIN Tablets are indicated for the treatment of patients with mild to moderate infections caused by susceptible strains of the designated microorganisms in the conditions listed below:

1. **Pharyngitis/Tonsillitis** caused by *Streptococcus pyogenes.*

   NOTE: The usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever, is penicillin given by the intramuscular route. CEFTIN Tablets are generally effective in the eradication of streptococci from the nasopharynx; however, substantial data establishing the efficacy of cefuroxime in the subsequent prevention of rheumatic fever are not available. Please also note that in all clinical trials, all isolates had to be sensitive to both penicillin and cefuroxime. There are no data from adequate and well-controlled trials to demonstrate the effectiveness of cefuroxime in the treatment of penicillin-resistant strains of *Streptococcus pyogenes.*

2. **Acute Bacterial Otitis Media** caused by *Streptococcus pneumoniae*, *Haemophilus influenzae* (including beta-lactamase–producing strains), *Moraxella catarrhalis* (including beta-lactamase–producing strains), or *Streptococcus pyogenes.*

3. **Acute Bacterial Maxillary Sinusitis** caused by *Streptococcus pneumoniae* or *Haemophilus influenzae* (non-beta-lactamase–producing strains only). (See CLINICAL STUDIES section.)

   NOTE: In view of the insufficient numbers of isolates of beta-lactamase–producing strains of *Haemophilus influenzae* and *Moraxella catarrhalis* that were obtained from clinical trials with CEFTIN Tablets for patients with acute bacterial maxillary sinusitis, it was not possible to adequately evaluate the

effectiveness of CEFTIN Tablets for sinus infections known, suspected, or considered potentially to be caused by beta-lactamase–producing *Haemophilus influenzae* or *Moraxella catarrhalis.*

4. **Acute Bacterial Exacerbations of Chronic Bronchitis and Secondary Bacterial Infections of Acute Bronchitis** caused by *Streptococcus pneumoniae*, *Haemophilus influenzae* (beta-lactamase negative strains), or *Haemophilus parainfluenzae* (beta-lactamase negative strains). (See DOSAGE AND ADMINISTRATION section and CLINICAL STUDIES section.)
5. **Uncomplicated Skin and Skin-Structure Infections** caused by *Staphylococcus aureus* (including beta-lactamase–producing strains) or *Streptococcus pyogenes.*
6. **Uncomplicated Urinary Tract Infections** caused by *Escherichia coli* or *Klebsiella pneumoniae.*
7. **Uncomplicated Gonorrhea,** urethral and endocervical, caused by penicillinase-producing and non-penicillinase–producing strains of *Neisseria gonorrhoeae* and uncomplicated gonorrhea, rectal, in females, caused by non-penicillinase–producing strains of *Neisseria gonorrhoeae.*
8. **Early Lyme Disease (erythema migrans)** caused by *Borrelia burgdorferi.*

CEFTIN for Oral Suspension: CEFTIN for Oral Suspension is indicated for the treatment of pediatric patients 3 months to 12 years of age with mild to moderate infections caused by susceptible strains of the designated microorganisms in the conditions listed below. The safety and effectiveness of CEFTIN for Oral Suspension in the treatment of infections other than those specifically listed below have not been established either by adequate and well-controlled trials or by pharmacokinetic data with which to determine an effective and safe dosing regimen.

1. **Pharyngitis/Tonsillitis** caused by *Streptococcus pyogenes.*

   NOTE: The usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever, is penicillin given by the intramuscular route. CEFTIN for Oral Suspension is generally effective in the eradication of streptococci from the nasopharynx; however, substantial data establishing the efficacy of cefuroxime in the subsequent prevention of rheumatic fever are not available. Please also note that in all clinical trials, all isolates had to be sensitive to both penicillin and cefuroxime. There are no data from adequate and well-controlled trials to demonstrate the effectiveness of cefuroxime in the treatment of penicillin-resistant strains of *Streptococcus pyogenes.*
2. **Acute Bacterial Otitis Media** caused by *Streptococcus pneumoniae*, *Haemophilus influenzae* (including beta-lactamase–producing strains), *Moraxella catarrhalis* (including beta-lactamase–producing strains), or *Streptococcus pyogenes.*
3. **Impetigo** caused by *Staphylococcus aureus* (including beta-lactamase–producing strains) or *Streptococcus pyogenes.*

Culture and susceptibility testing should be performed when appropriate to determine susceptibility of the causative microorganism(s) to cefuroxime. Therapy may be started while awaiting the results of this testing. Antimicrobial therapy should be appropriately adjusted according to the results of such testing.

CONTRAINDICATIONS: CEFTIN products are contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

WARNINGS: CEFTIN TABLETS AND CEFTIN FOR ORAL SUSPENSION ARE NOT BIOEQUIVALENT AND ARE THEREFORE NOT SUBSTITUTABLE ON A MG/MG BASIS (SEE CLINICAL PHARMACOLOGY).

BEFORE THERAPY WITH CEFTIN PRODUCTS IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEFTIN PRODUCTS, OTHER CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. IF THIS PRODUCT IS TO BE GIVEN TO PENICILLIN-SENSITIVE PATIENTS, CAUTION SHOULD BE EXERCISED BECAUSE CROSS-HYPERSENSITIVITY AMONG BETA-LACTAM ANTIBIOTICS HAS BEEN CLEARLY DOCUMENTED AND MAY OCCUR IN UP TO 10% OF PATIENTS WITH A HISTORY OF PENICILLIN ALLERGY. IF A CLINICALLY SIGNIFICANT ALLERGIC REACTION TO CEFTIN PRODUCTS OCCURS, DISCONTINUE THE DRUG AND INSTITUTE APPROPRIATE THERAPY. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE TREATMENT WITH EPINEPHRINE AND OTHER EMERGENCY MEASURES, INCLUDING OXYGEN, INTRAVENOUS FLUIDS, INTRAVENOUS ANTIHISTAMINES, CORTICOSTEROIDS, PRESSOR AMINES, AND AIRWAY MANAGEMENT, AS CLINICALLY INDICATED.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including cefuroxime, and may range from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis.

After the diagnosis of pseudomembranous colitis has been established, appropriate therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug effective against *Clostridium difficile*.

PRECAUTIONS:

General: As with other broad-spectrum antibiotics, prolonged administration of cefuroxime axetil may result in overgrowth of nonsusceptible microorganisms. If superinfection occurs during therapy, appropriate measures should be taken.

Cephalosporins, including cefuroxime axetil, should be given with caution to patients receiving concurrent treatment with potent diuretics because these diuretics are suspected of adversely affecting renal function.

Cefuroxime axetil, as with other broad-spectrum antibiotics, should be prescribed with caution in individuals with a history of colitis. The safety and effectiveness of cefuroxime axetil have not been established in patients with gastrointestinal malabsorption. Patients with gastrointestinal malabsorption were excluded from participating in clinical trials of cefuroxime axetil.

Cephalosporins may be associated with a fall in prothrombin activity. Those at risk include patients with renal or hepatic impairment, or poor nutritional state, as well as patients receiving a protracted course of antimicrobial therapy, and patients previously stabilized on anticoagulant therapy. Prothrombin time should be monitored in patients at risk and exogenous Vitamin K administered as indicated.

Information for Patients/Caregivers (Pediatric): 1. During clinical trials, the tablet was tolerated by pediatric patients old enough to swallow the cefuroxime axetil tablet whole. The crushed tablet has a strong, persistent, bitter taste and should not be administered to pediatric patients in this manner. Pediatric patients who cannot swallow the tablet whole should receive the oral suspension.

2. Discontinuation of therapy due to taste and/or problems of administering this drug occurred in 1.4% of pediatric patients given the oral suspension. Complaints about taste (which may impair compliance) occurred in 5% of pediatric patients.

Drug/Laboratory Test Interactions: A false-positive reaction for glucose in the urine may occur with copper reduction tests (Benedict's or Fehling's solution or with CLINITEST® tablets), but not with enzyme-based tests for glycosuria (e.g., CLINISTIX®, TES-TAPE®). As a false-negative result may occur in the ferricyanide test, it is recommended that either the glucose oxidase or hexokinase method be used to determine blood/plasma glucose levels in patients receiving cefuroxime axetil. The presence of cefuroxime does not interfere with the assay of serum and urine creatinine by the alkaline picrate method.

Drug/Drug Interactions: Concomitant administration of probenecid with cefuroxime axetil tablets increases the area under the serum concentration versus time curve by 50%. The peak serum cefuroxime concentration after a 1.5-g single dose is greater when taken with 1 g of probenecid (mean = 14.8 mcg/mL) than without probenecid (mean = 12.2 mcg/mL).

Drugs that reduce gastric acidity may result in a lower bioavailability of CEFTIN compared with that of fasting state and tend to cancel the effect of postprandial absorption.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Although lifetime studies in animals have not been performed to evaluate carcinogenic potential, no mutagenic activity~~potential~~ was found for cefuroxime axetil in a battery of bacterial mutation tests. Positive results were obtained in an *in vitro* chromosome aberration assay, however, negative results were found in an *in vivo* micronucleus test at doses up to 1.5 g/kg.~~the micronucleus test and a battery of bacterial mutation tests.~~ Reproduction studies in rats at doses up to 1000 mg/kg per day (~~nine~~ 9 times the recommended maximum human dose based on mg/m^2) have revealed no ~~evidence~~ impairment of ~~impaired~~ fertility.

Pregnancy: ***Teratogenic Effects:*** Pregnancy Category B. Reproduction studies have been performed in ~~rats and~~ mice at doses up to 3200 mg/kg per day (~~23~~14 times the recommended maximum human dose based on mg/m^2) and in rats at doses up to 1000 mg/kg per day (9 times the recommended maximum human dose based on mg/m^2)and have revealed no evidence of impaired fertility or harm to the fetus due to cefuroxime axetil. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery: Cefuroxime axetil has not been studied for use during labor and delivery.

Nursing Mothers: Because cefuroxime is excreted in human milk, consideration should be given to discontinuing nursing temporarily during treatment with cefuroxime axetil.

Pediatric Use: The safety and effectiveness of CEFTIN have been established for pediatric patients aged 3 months to 12 years for acute bacterial maxillary sinusitis based upon its approval in adults. Use of CEFTIN in pediatric patients is supported by pharmacokinetic and safety data in adults and pediatric patients, and by clinical and microbiological data from adequate and well-controlled studies of the treatment of acute bacterial maxillary sinusitis in adults and of acute otitis media with effusion in pediatric patients. It is also supported by post-marketing adverse events surveillance (see CLINICAL PHARMACOLOGY, INDICATIONS AND USAGE, ADVERSE REACTIONS, DOSAGE AND ADMINISTRATION, and CLINICAL STUDIES).

Geriatric Use: In clinical trials when 12- to 64-year-old patients and geriatric patients (65 years of age or older) were treated with usual recommended dosages (i.e., 125 to 500 mg b.i.d., depending on type of infections), no overall differences in effectiveness were observed between the ~~two~~ 2 age-groups. The geriatric patients reported somewhat fewer gastrointestinal events and less frequent vaginal candidiasis compared with patients aged 12 to 64 years old; however, no clinically significant differences were reported between the ~~two~~ 2 age-groups. Therefore, no adjustment of the usual adult dose is necessary based on age alone.

ADVERSE REACTIONS:

CEFTIN TABLETS IN CLINICAL TRIALS: Multiple-Dose Dosing Regimens: ***7 to 10 Days Dosing:*** Using multiple doses of cefuroxime axetil tablets, 912 patients were treated with the recommended dosages of cefuroxime axetil (125 to 500 mg twice a day). There were no deaths or permanent disabilities thought related to drug toxicity. Twenty (2.2%) patients discontinued medication due to adverse events thought by the investigators to be possibly, probably, or almost certainly related to drug toxicity. Seventeen (85%) of the 20 patients who discontinued therapy did so because of gastrointestinal disturbances, including diarrhea, nausea, vomiting, and abdominal pain. The percentage of cefuroxime axetil tablet-treated patients who discontinued study drug because of adverse events was very similar at daily doses of 1000, 500, and 250 mg (2.3%, 2.1%, and 2.2%, respectively). However, the incidence of gastrointestinal adverse events increased with the higher recommended doses.

The following adverse events were thought by the investigators to be possibly, probably, or almost certainly related to cefuroxime axetil tablets in multiple-dose clinical trials (n = 912 cefuroxime axetil-treated patients).

Table 4: Adverse Reactions

CEFTIN Tablets

Multiple-Dose Dosing Regimens—Clinical Trials

Incidence ≥1%	Diarrhea/loose stools	3.7%
	Nausea/vomiting	3.0%
	Transient elevation in AST	2.0%
	Transient elevation in ALT	1.6%
	Eosinophilia	1.1%
	Transient elevation in LDH	1.0%
Incidence	Abdominal pain	
<1% but >0.1%	Abdominal cramps	
	Flatulence	
	Indigestion	
	Headache	
	Vaginitis	
	Vulvar itch	
	Rash	
	Hives	
	Itch	
	Dysuria	
	Chills	
	Chest Pain	
	Shortness of breath	
	Mouth ulcers	
	Swollen tongue	
	Sleepiness	
	Thirst	
	Anorexia	
	Positive Coombs' test	

5-Day Experience (see CLINICAL STUDIES section): In clinical trials using CEFTIN in a dose of 250 mg b.i.d. in the treatment of secondary bacterial infections of acute bronchitis, 399 patients were treated for 5 days and 402 patients were treated for 10 days. No difference in the occurrence of adverse events was found between the ~~two~~ 2 regimens.

In Clinical Trials for Early Lyme Disease With 20 Days Dosing: Two multicenter trials assessed cefuroxime axetil tablets 500 mg twice a day for 20 days. The most common drug-related adverse experiences were diarrhea (10.6% of patients), Jarisch-Herxheimer's reaction (5.6%), and vaginitis (5.4%). Other adverse experiences occurred with frequencies comparable to those reported with 7 to 10 days dosing.

Single-Dose Regimen for Uncomplicated Gonorrhea: In clinical trials using a single dose of cefuroxime axetil tablets, 1061 patients were treated with the recommended dosage of cefuroxime axetil (1000 mg) for the treatment of uncomplicated gonorrhea. There were no deaths or permanent disabilities thought related to drug toxicity in these studies.

The following adverse events were thought by the investigators to be possibly, probably, or almost certainly related to cefuroxime axetil in 1000-mg single-dose clinical trials of cefuroxime axetil tablets in the treatment of uncomplicated gonorrhea conducted in the US.

Table 5: Adverse Reactions

CEFTIN Tablets

1-g Single-Dose Regimen for Uncomplicated Gonorrhea—Clinical Trials

Incidence ≥1%	Nausea/vomiting	6.8%
	Diarrhea	4.2%
Incidence	Abdominal pain	
<1% but >0.1%	Dyspepsia	
	Erythema	
	Rash	
	Pruritus	
	Vaginal candidiasis	
	Vaginal itch	
	Vaginal discharge	
	Headache	
	Dizziness	
	Somnolence	
	Muscle cramps	
	Muscle stiffness	
	Muscle spasm of neck	
	Tightness/pain in chest	
	Bleeding/pain in urethra	
	Kidney pain	
	Tachycardia	
	Lockjaw-type reaction	

CEFTIN FOR ORAL SUSPENSION IN CLINICAL TRIALS: In clinical trials using multiple doses of cefuroxime axetil powder for oral suspension, pediatric patients (96.7% of whom were younger than 12 years of age) were treated with the recommended dosages of cefuroxime axetil (20 to 30 mg/kg per day divided twice a day up to a maximum dose of 500 or 1000 mg/day, respectively). There were no deaths or permanent disabilities in any of the patients in these studies. Eleven US patients (1.2%) discontinued medication due to adverse events thought by the investigators to be possibly, probably, or almost certainly related to drug toxicity. The discontinuations were primarily for gastrointestinal disturbances, usually diarrhea or vomiting. During clinical trials, discontinuation of therapy due to the taste and/or problems with administering this drug occurred in 13 (1.4%) pediatric patients enrolled at centers in the US.

The following adverse events were thought by the investigators to be possibly, probably, or almost certainly related to cefuroxime axetil for oral suspension in multiple-dose clinical trials (n = 931 cefuroxime axetil-treated US patients).

Table 6: Adverse Reactions
CEFTIN for Oral Suspension
Multiple-Dose Dosing Regimens—
Clinical Trials

Incidence ≥1%	Diarrhea/loose stools	8.6%
	Dislike of taste	5.0%
	Diaper rash	3.4%
	Nausea/vomiting	2.6%
Incidence <1% but >0.1%	Abdominal pain	
	Flatulence	
	Gastrointestinal infection	
	Candidiasis	
	Vaginal irritation	
	Rash	
	Hyperactivity	
	Irritable behavior	
	Eosinophilia	
	Positive direct Coombs' test	
	Elevated liver enzymes	
	Viral illness	
	Upper respiratory infection	
	Sinusitis	
	Cough	
	Urinary tract infection	
	Joint swelling	
	Arthralgia	
	Fever	
	Ptyalism	

POSTMARKETING EXPERIENCE WITH CEFTIN PRODUCTS:~~OBSERVED DURING CLINICAL PRACTICE:~~ In addition to adverse events reported ~~from~~ during clinical trials, the following events have been

identified during clinical practice in patients treated with ~~during post-approval use of~~ CEFTIN Tablets or with CEFTIN for Oral Suspension and were reported spontaneously. Data are generally insufficient to allow an estimate of incidence or to establish causation. ~~Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to combination of their seriousness, frequency of reporting, or potential causal connection to CEFTIN.~~

~~**Blood and Lymphatic:** Increased prothrombin time.~~

General: The following hypersensitivity reactions have been reported: anaphylaxis, angioedema, pruritus, rash, serum sickness-like reaction, and urticaria.

Gastrointestinal: Pseudomembranous colitis (see WARNINGS).

Hematologic: Hemolytic anemia, leukopenia, pancytopenia, ~~and~~ thrombocytopenia, and increased prothrombin time.

Hepatic~~Hepatobiliary Tract and Pancreas~~: Hepatic impairment including hepatitis and cholestasis, jaundice.

Neurologic: Seizure.

Skin: Erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis.

Urologic: Renal dysfunction.

CEPHALOSPORIN-CLASS ADVERSE REACTIONS: In addition to the adverse reactions listed above that have been observed in patients treated with cefuroxime axetil, the following adverse reactions and altered laboratory tests have been reported for cephalosporin-class antibiotics: ~~renal dysfunction,~~ toxic nephropathy, ~~hepatic cholestasis,~~ aplastic anemia, ~~hemolytic anemia,~~ hemorrhage, ~~increased prothrombin time,~~ increased BUN, increased creatinine, false-positive test for urinary glucose, increased alkaline phosphatase, neutropenia, ~~thrombocytopenia, leukopenia,~~ elevated bilirubin, ~~pancytopenia,~~ and agranulocytosis.

Several cephalosporins have been implicated in triggering seizures, particularly in patients with renal impairment when the dosage was not reduced (see DOSAGE AND ADMINISTRATION and OVERDOSAGE). If seizures associated with drug therapy occur, the drug should be discontinued. Anticonvulsant therapy can be given if clinically indicated.

OVERDOSAGE: Overdosage of cephalosporins can cause cerebral irritation leading to convulsions. Serum levels of cefuroxime can be reduced by hemodialysis and peritoneal dialysis.

DOSAGE AND ADMINISTRATION:

NOTE: CEFTIN TABLETS AND CEFTIN FOR ORAL SUSPENSION ARE NOT BIOEQUIVALENT AND ARE NOT SUBSTITUTABLE ON A MG/MG BASIS (SEE CLINICAL PHARMACOLOGY).

Table 7: CEFTIN Tablets

(May be administered without regard to meals.)

Population/Infection	Dosage	Duration (days)
Adolescents and Adults (13 years and older)		
Pharyngitis/tonsillitis	250 mg b.i.d.	10
Acute bacterial maxillary sinusitis	250 mg b.i.d.	10
Acute bacterial exacerbations of chronic bronchitis	250 or 500 mg b.i.d.	10*
Secondary bacterial infections of acute bronchitis	250 or 500 mg b.i.d.	5-10
Uncomplicated skin and skin-structure infections	250 or 500 mg b.i.d.	10
Uncomplicated urinary tract infections	125 or 250 mg b.i.d.	7-10
Uncomplicated gonorrhea	1000 mg once	single dose
Early Lyme disease	500 mg b.i.d.	20
Pediatric Patients (who can swallow tablets whole)		
Pharyngitis/tonsillitis	125 mg b.i.d.	10
Acute otitis media	250 mg b.i.d.	10
Acute bacterial maxillary sinusitis	250 mg b.i.d.	10

*The safety and effectiveness of CEFTIN administered for less than 10 days in patients with acute exacerbations of chronic bronchitis have not been established.

CEFTIN for Oral Suspension: CEFTIN for Oral Suspension may be administered to pediatric patients ranging in age from 3 months to 12 years, according to dosages in Table 8:

Table 8: CEFTIN for Oral Suspension

(Must be administered with food. Shake well each time before using.)

Population/Infection	Dosage	Daily Maximum Dose	Duration (days)
Pediatric Patients (3 months to 12 years)			
Pharyngitis/tonsillitis	20 mg/kg/day divided b.i.d.	500 mg	10
Acute otitis media	30 mg/kg/day divided b.i.d.	1000 mg	10
Acute bacterial maxillary sinusitis	30 mg/kg/day divided b.i.d.	1000 mg	10
Impetigo	30 mg/kg/day divided b.i.d.	1000 mg	10

Patients With Renal Failure: The safety and efficacy of cefuroxime axetil in patients with renal failure have not been established. Since cefuroxime is renally eliminated, its half-life will be prolonged in patients with renal failure.

Directions for Mixing CEFTIN for Oral Suspension: Prepare a suspension at the time of dispensing as follows:

1. Shake the bottle to loosen the powder.
2. Remove the cap.
3. Add the total amount of water for reconstitution (see Table 9) and replace the cap.
4. Invert the bottle and vigorously rock the bottle from side to side so that water rises through the powder.
5. Once the sound of the powder against the bottle disappears, turn the bottle upright and vigorously shake it in a diagonal direction.

Table 9: Amount of Water Required for Reconstitution of Labeled Volumes of CEFTIN for Oral Suspension

CEFTIN for Oral Suspension	Labeled Volume After Reconstitution	Amount of Water Required for Reconstitution
125 mg/5 mL	50 mL	20 mL
	100 mL	37 mL
250 mg/5 mL	50 mL	19 mL
	100 mL	35 mL

NOTE: SHAKE THE ORAL SUSPENSION WELL BEFORE EACH USE. Replace cap securely after each opening. The reconstituted suspension should be stored between 2° and 25°C (36° and 77°F) (either in the refrigerator or at room temperature). DISCARD AFTER 10 DAYS.

HOW SUPPLIED:

CEFTIN Tablets: CEFTIN Tablets, 125 mg of cefuroxime (as cefuroxime axetil), are white, capsule-shaped, film-coated tablets engraved with "395" on one side and "Glaxo" on the other side as follows:

20 Tablets/Bottle NDC 0173-0395-00
60 Tablets/Bottle NDC 0173-0395-01
Unit Dose Packs of 100 NDC 0173-0395-02

CEFTIN Tablets, 250 mg of cefuroxime (as cefuroxime axetil), are light blue, capsule-shaped, film-coated tablets engraved with "387" on one side and "Glaxo" on the other side as follows:

20 Tablets/Bottle NDC 0173-0387-00
60 Tablets/Bottle NDC 0173-0387-42

Unit Dose Packs of 100 NDC 0173-0387-01

CEFTIN Tablets, 500 mg of cefuroxime (as cefuroxime axetil), are dark blue, capsule-shaped, film-coated tablets engraved with "394" on one side and "Glaxo" on the other side as follows:

20 Tablets/Bottle NDC 0173-0394-00

60 Tablets/Bottle NDC 0173-0394-42

Unit Dose Packs of 50 NDC 0173-0394-01

Store the tablets between 15° and 30°C (59° and 86°F). Replace cap securely after each opening. Protect unit dose packs from excessive moisture.

CEFTIN for Oral Suspension: CEFTIN for Oral Suspension is provided as dry, white to pale yellow, tutti-frutti–flavored powder. When reconstituted as directed, CEFTIN for Oral Suspension provides the equivalent of 125 mg or 250 mg of cefuroxime (as cefuroxime axetil) per 5 mL of suspension. It is supplied in amber glass bottles as follows:

125 mg/5 mL:

50-mL Suspension NDC 0173-0406-01

100-mL Suspension NDC 0173-0406-00

250 mg/5 mL:

50-mL Suspension NDC 0173-0554-00

100-mL Suspension NDC 0173-0555-00

Before reconstitution, store dry powder between 2° and 30°C (36° and 86°F).

After reconstitution, store suspension between 2° and 25°C (36° and 77°F), in a refrigerator or at room temperature. DISCARD AFTER 10 DAYS.

CLINICAL STUDIES:

CEFTIN Tablets: ***Acute Bacterial Maxillary Sinusitis:*** One adequate and well-controlled study was performed in patients with acute bacterial maxillary sinusitis. In this study each patient had a maxillary sinus aspirate collected by sinus puncture before treatment was initiated for presumptive acute bacterial sinusitis. All patients had to have radiographic and clinical evidence of acute maxillary sinusitis. As shown in the following summary of the study, the general clinical effectiveness of CEFTIN Tablets was comparable to an oral antimicrobial agent that contained a specific beta-lactamase inhibitor in treating acute maxillary sinusitis. However, sufficient microbiology data were obtained to demonstrate the effectiveness of CEFTIN Tablets in treating acute bacterial maxillary sinusitis due only to *Streptococcus pneumoniae* or non-beta-lactamase–producing *Haemophilus influenzae*. An insufficient number of beta-lactamase–producing *Haemophilus influenzae* and *Moraxella catarrhalis* isolates were obtained in this trial to adequately evaluate the effectiveness of CEFTIN Tablets in the treatment of acute bacterial maxillary sinusitis due to these ~~two~~ 2 organisms.

This study enrolled 317 adult patients, 132 patients in the United States and 185 patients in South America. Patients were randomized in a 1:1 ratio to cefuroxime axetil 250 mg b.i.d. or an oral antimicrobial agent that contained a specific beta-lactamase inhibitor. An intent-to-treat analysis of the submitted clinical data yielded the following results:

Table 10: Clinical Effectiveness of CEFTIN Tablets Compared to Beta-Lactamase Inhibitor-Containing Control Drug in the Treatment of Acute Bacterial Maxillary Sinusitis

	US Patients*		South American Patients†	
	CEFTIN n = 49	Control n = 43	CEFTIN n = 87	Control n = 89
Clinical success (cure + improvement)	65%	53%	77%	74%
Clinical cure	53%	44%	72%	64%
Clinical improvement	12%	9%	5%	10%

* 95% Confidence interval around the success difference [-0.08, +0.32].

† 95% Confidence interval around the success difference [-0.10, +0.16].

In this trial and in a supporting maxillary puncture trial, 15 evaluable patients had non-beta-lactamase–producing *Haemophilus influenzae* as the identified pathogen. Ten (10) of these 15 patients (67%) had their pathogen (non-beta-lactamase–producing *Haemophilus influenzae*) eradicated. Eighteen (18) evaluable patients had *Streptococcus pneumoniae* as the identified pathogen. Fifteen (15) of these 18 patients (83%) had their pathogen (*Streptococcus pneumoniae*) eradicated.

Safety: The incidence of drug-related gastrointestinal adverse events was statistically significantly higher in the control arm (an oral antimicrobial agent that contained a specific beta-lactamase inhibitor) versus the cefuroxime axetil arm (12% versus 1%, respectively; $P<0.001$), particularly drug-related diarrhea (8% versus 1%, respectively; $P = 0.001$).

Early Lyme Disease: Two adequate and well-controlled studies were performed in patients with early Lyme disease. In these studies all patients had to present with physician-documented erythema migrans, with or without systemic manifestations of infection. Patients were randomized in a 1:1 ratio to a 20-day course of treatment with cefuroxime axetil 500 mg b.i.d. or doxycycline 100 mg t.i.d. Patients were assessed at 1 month posttreatment for success in treating early Lyme disease (Part I) and at 1 year posttreatment for success in preventing the progression to the sequelae of late Lyme disease (Part II).

A total of 355 adult patients (181 treated with cefuroxime axetil and 174 treated with doxycycline) were enrolled in the ~~two~~ 2 studies. In order to objectively validate the clinical diagnosis of early Lyme disease in these patients, ~~two~~ 2 approaches were used: 1) blinded expert reading of photographs, when available, of

the pretreatment erythema migrans skin lesion; and 2) serologic confirmation (using enzyme-linked immunosorbent assay [ELISA] and immunoblot assay ["Western" blot]) of the presence of antibodies specific to *Borrelia burgdorferi*, the etiologic agent of Lyme disease. By these procedures, it was possible to confirm the physician diagnosis of early Lyme disease in 281 (79%) of the 355 study patients. The efficacy data summarized below are specific to this "validated" patient subset, while the safety data summarized below reflect the entire patient population for the ~~two~~ 2 studies.

Analysis of the submitted clinical data for evaluable patients in the "validated" patient subset yielded the following results:

Table 11: Clinical Effectiveness of CEFTIN Tablets Compared to Doxycycline in the Treatment of Early Lyme Disease

	Part I (1 Month Posttreatment)*		Part II (1 Year Posttreatment)†	
	CEFTIN n = 125	Doxycycline n = 108	CEFTIN n = 105‡	Doxycycline n = 83‡
Satisfactory clinical outcome§	91%	93%	84%	87%
Clinical cure/success	72%	73%	73%	73%
Clinical improvement	19%	19%	10%	13%

* 95% confidence interval around the satisfactory difference for Part I (-0.08, +0.05).

† 95% confidence interval around the satisfactory difference for Part II (-0.13, +0.07).

‡ n's include patients assessed as unsatisfactory clinical outcomes (failure + recurrence) in Part I (CEFTIN - 11 [5 failure, 6 recurrence]; doxycycline - 8 [6 failure, 2 recurrence]).

§ Satisfactory clinical outcome includes cure + improvement (Part I) and success + improvement (Part II).

CEFTIN and doxycycline were effective in prevention of the development of sequelae of late Lyme disease.

Safety: Drug-related adverse events affecting the skin were reported significantly more frequently by patients treated with doxycycline than by patients treated with cefuroxime axetil (12% versus 3%, respectively; $P = 0.002$), primarily reflecting the statistically significantly higher incidence of drug-related photosensitivity reactions in the doxycycline arm versus the cefuroxime axetil arm (9% versus 0%, respectively; $P<0.001$). While the incidence of drug-related gastrointestinal adverse events was similar in the ~~two~~ 2 treatment groups (cefuroxime axetil - 13%; doxycycline - 11%), the incidence of drug-related diarrhea was statistically significantly higher in the cefuroxime axetil arm versus the doxycycline arm (11% versus 3%, respectively; $P = 0.005$).

Secondary Bacterial Infections of Acute Bronchitis: Four randomized, controlled clinical studies were performed comparing 5 days versus 10 days of CEFTIN for the treatment of patients with secondary bacterial infections of acute bronchitis. These studies enrolled a total of 1253 patients (CAE-516 n = 360; CAE-517 n = 177; CAEA4001 n = 362; CAEA4002 n = 354). The protocols for CAE-516 and CAE-517 were identical and compared CEFTIN 250 mg b.i.d. for 5 days, CEFTIN 250 mg b.i.d. for 10 days, and AUGMENTIN® 500 mg t.i.d. for 10 days. These ~~two~~ 2 studies were conducted simultaneously. CAEA4001 and CAEA4002 compared CEFTIN 250 mg b.i.d. for 5 days, CEFTIN 250 mg b.i.d. for 10 days, and CECLOR® 250 mg t.i.d. for 10 days. They were otherwise identical to CAE-516 and CAE-517 and were conducted over the following ~~two~~ 2 years. Patients were required to have polymorphonuclear cells present on the Gram stain of their screening sputum specimen, but isolation of a bacterial pathogen from the sputum culture was not required for inclusion. The following table demonstrates the results of the clinical outcome analysis of the pooled studies CAE-516/CAE-517 and CAEA4001/CAEA4002, respectively:

Table 12: Clinical Effectiveness of CEFTIN Tablets 250 mg b.i.d. in Secondary Bacterial Infections of Acute Bronchitis: Comparison of 5 Versus 10 Days' Treatment Duration

	CAE-516 and CAE-517*		CAEA4001 and CAEA4002†	
	5 Day (n = 127)	10 Day (n = 139)	5 Day (n = 173)	10 Day (n = 192)
Clinical success (cure + improvement)	80%	87%	84%	82%
Clinical cure	61%	70%	73%	72%
Clinical improvement	19%	17%	11%	10%

* 95% Confidence interval around the success difference [-0.164, +0.029].

† 95% Confidence interval around the success difference [-0.061, +0.103].

The response rates for patients who were both clinically and bacteriologically evaluable were consistent with those reported for the clinically evaluable patients.

Safety: In these clinical trials, 399 patients were treated with CEFTIN for 5 days and 402 patients with CEFTIN for 10 days. No difference in the occurrence of adverse events was observed between the ~~two~~ 2 regimens.

REFERENCES:

1. National Committee for Clinical Laboratory Standards. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically.* 3rd ed. Approved Standard NCCLS Document M7-A3, Vol. 13, No. 25. Villanova, Pa: NCCLS; 1993.

2. National Committee for Clinical Laboratory Standards. *Performance Standards for Antimicrobial Disk Susceptibility Tests.* 4th ed. Approved Standard NCCLS Document M2-A4, Vol. 10, No. 7. Villanova, Pa: NCCLS; 1990.

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Janice Soreth

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